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Synthesis and Antifungal Activity of Dithiocarbamoic Acid Derivatives

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Abstract

Dithiocarbamoic acid and their derivatives were found to readily react with potassium and sodium hydroxide to give the corresponding alkali metal dithiocarbamoic acid derivatives **8-17** in moderate to good yields.

Key words : Dithiocarbamate, Chelating effect, Coordination chemistry, Alkali metal salts.

1. Introduction

Coumarin derivatives have been reported to possess a wide variety of pharmacological activities such as anticoagulant[1,2], fungicidal[3,4], tuberculostatic and diuretic[5]. On the other hand, antifungal and antibacterial activities of *N*-substituted and *N*,*N*-disubstituted dithiocarbamoic acid derivatives are well known[6,7]. Previous publications from Kiraz and co-workers[8] have dealt with the synthesis of a series of 4-[(*N*,*N*-disubstituted thiocarbamoylthio)acyl]antipyrines and 4-[(*N*,*N*-disubstituted thiocarbamoylthio)acetamido]antipyrines, some of which are endowed with significant antifungal activity. In view of this observation we synthesized new 3-[(*N*,*N*-disubstituted thiocarbamoylthio)acetyl]coumarins and tested them for antifungal activity.

2. Results and Discussion

The antifungal activity of the compounds was evaluated against seven representative fungi and compared with that of clotrimazole and miconazole. None of them showed comparable activity to the standards against tested fungi (Table 1).

2.2. Chemistry

The reaction of 3-(*o*-bromoacetyl)coumarins (**6** and **7**) with potassium salts of dithiocarbamic acids (**1-5**, Scheme 1) which were obtained by literature methods[9,10] afforded in ethanolic medium 3-[(*N*,*N*-disubstituted carbamoildithiolato)acetyl]coumarin derivatives (**8-17**) (Scheme 2).

Analytical and spectral data (IR, ^{1}H, ^{13}C-NMR, elemental analysis) confirmed the structures of **8-17**. IR spectra of **8-17** showed C=O lacton stretching of the coumarin residue around 1744-1715 cm^1, α,β-unsaturated ketone C=O stretching in the region of 1695-1653 cm^1 and thiocarbonyl group C=S stretching at about 1255-1228 cm^1. In the ^{1}H-NMR spectra, the C4*H* proton of the coumarin moiety and the COCH_2 protons appeared at about 8.48-8.68 and 4.81-4.90 ppm, respectively.

2.3. Pharmacology

Antifungal activities were investigated against Trichophyton tonsurans NCPF 245, Microsporum gypseum NCPF 580, and Trichophyton mentagrophytes var erinacei ATCC 375 using the microdilution method.

3. Experimentals

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer and the chemical shifts are referenced to internal solvent resonances. IR spectra were recorded on a Bruker VECTOR-22 spectrometer. Elemental analyses were performed with a Carlo Erba Instruments CHNS-O EA1108 analyzer. Melting points were uncorrected.

General Procedure for the Synthesis of 1-5. KOH (10 mmol) was dissolved in EtOH (100 mL) with constant stirring. After addition of the secondary amine

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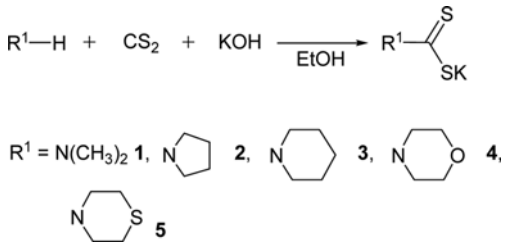
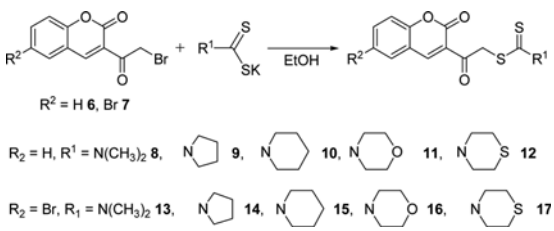


Scheme 1. Synthesis of *N*,*N*-disubstituted dithiocarbamic acid derivatives (**1-5**).



Scheme 2. Synthesis of [(*N*,*N*-disubstituted carbamoildithiolato)acetyl]coumarin derivatives (**8-17**).

(10 mmol) the mixture was cooled in an ice bath and CS_2 (10 mmol) was added dropwise with stirring. The reaction mixture thus obtained was further agitated for 1 h at room temperature; after evaporation of the solvent under reduced pressure and consequent addition of dry ether until precipitation reached completion, filtration afforded **1-5** which were either recrystallized from EtOH or used without further purification.

General Procedure for the Synthesis of 8-17. To an ethanolic solution of **6** or **7** (10 mmol), **15** (10 mmol) was added and the reaction mixture refluxed for 1 h. After cooling the solution was evaporated to dryness under reduced pressure and the products were washed with water and purified by recrystallization from ethanol.

8. Yield: 85%. Mp. 168-170°C. Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.35; H, 4.89; N, 4.53. Found: C, 54.58; H, 4.99; N, 4.47%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1744, ν(C=O) 1694, ν(C=S) 1252. ^{1}H NMR ($CDCl_3$) δ 8.52 (s, lH, coum C4-*H*), 7.65 (d, lH, *J* = 7 Hz, coum C5-*H*), 7.64 (t, lH, *J* = 8 Hz, coum C7-*H*), 7.36 (t, lH, *J* = 8 Hz, coum C6-*H*), 7.31 (d, lH, *J* = 7 Hz, coum C8-*H*), 4.80 (s, 2H, COC*H*,), 3.84, 3.76 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.12-1.96 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 206.7, 197.1, 169.3, 149.6, 133.2, 127.1, 126.1, 125.3, 122.5, 60.9, 43.1, 41.8, 31.2.

Table 1. MIC values (mg/mL) of **8-17**.

Compound	Fungi		
	NCPF 245	NCPF 580	ATCC 375
8	25	25	25
9	25	25	>25
10	12.5	25	>25
11	25	25	>25
12	25	25	>25
13	25	25	>25
14	25	25	25
15	25	25	25
16	25	25	>25
17	25	25	>25
Miconazole	0.2	0.2	0.2
Chlotrimazole	0.2	0.2	0.2

9. Yield: 100%. Mp. 187-189°C. Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.29; H, 5.11; N, 4.18. Found: C, 58.01; H, 5.31; N, 4.41%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1720, ν(C=O) 1690, ν(C=S) 1250. ^{1}H NMR ($CDCl_3$) δ 8.50 (s, lH, coum C4-*H*), 7.66 (d, lH, *J* = 7 Hz, coum C5-*H*), 7.64 (t, lH, *J* = 8 Hz, coum C7-*H*), 7.37 (t, lH, *J* = 8 Hz, coum C6-*H*), 7.33 (d, lH, *J* = 7 Hz, coum C8-*H*), 4.82 (s, 2H, COC*H*,), 3.86, 3.74 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.11-1.98 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 207.1, 197.7, 169.0, 149.0, 133.0, 128.1, 126.4, 125.5, 121.5, 59.9, 52.7, 29.5, 24.7.

10. Yield: 89%. Mp. 179-180°C. Anal. Calcd for $C_{17}H_{19}NO_3S_2$: C, 58.43; H, 5.48; N, 4.01. Found: C, 58.04; H, 5.87; N, 4.33%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1731, ν(C=O) 1688, ν(C=S) 1249. ^{1}H NMR ($CDCl_3$) δ 8.47 (s, lH, coum C4-*H*), 7.41 (d, lH, *J* = 7 Hz, coum C5-*H*), 7.38 (t, lH, *J* = 8 Hz, coum C7-*H*), 7.35 (t, lH, *J* = 8 Hz, coum C6-*H*), 7.27 (d, lH, *J* = 7 Hz, coum C8-*H*), 4.77 (s, 2H, COC*H*,), 3.71, 3.66 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.20-2.11 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 206.5, 198.7, 171.0, 152.0, 128.8, 126.8, 124.3, 122.2, 120.0, 59.9, 48.6, 42.7, 25.4, 24.1.

11. Yield: 86%. Mp. 163-164°C. Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.88; N, 3.99. Found: C, 54.88; H, 4.98; N, 4.21%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1740, ν(C=O) 1679, ν(C=S) 1234. ^{1}H NMR ($CDCl_3$) δ 8.67 (s, lH, coum C4-*H*), 7.84 (d, lH, *J* = 7

Hz, coum C5-*H*), 7.71 (t, lH, *J* = 8 Hz, coum C7-*H*), 7.42 (t, lH, *J* = 8 Hz, coum C6-*H*), 7.38 (d, lH, *J* = 7 Hz, coum C8-*H*), 5.01 (s, 2H, COC*H*,), 4.03, 3.88 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.34-2.03 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 207.5, 195.4, 168.5, 151.6, 138.0, 128.8, 127.4, 124.1, 121.1, 65.8, 49.4, 42.8, 30.1.

12. Yield: 87%. Mp. 166-168°C. Anal. Calcd for $C_{16}H_{17}NO_3S_3$: C, 52.29; H, 4.66; N, 3.81. Found: C, 53.10; H, 4.41; N, 3.68%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1732, ν(C=O) 1679, ν(C=S) 1244. ^{1}H NMR ($CDCl_3$) δ 8.74 (s, lH, coum C4-*H*), 7.55 (d, lH, *J* = 7 Hz, coum C5-*H*), 7.54 (t, lH, *J* = 8 Hz, coum C7-*H*), 7.35 (t, lH, *J* = 8 Hz, coum C6-*H*), 7.30 (d, lH, *J* = 7 Hz, coum C8-*H*), 4.79 (s, 2H, COCH,), 3.75, 3.71 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.21-2.07 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 208.3, 196.7, 169.7, 151.3, 135.7, 130.0, 127.1, 126.3, 120.7, 49.8, 40.8, 27.1.

13. Yield: 93%. Mp. 186-188°C. Anal. Calcd for $C_{14}H_{14}BrNO_3S_2$: C, 43.30; H, 3.63; N, 3.61. Found: C, 43.84; H, 3.89; N, 3.51%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1744, ν(C=O) 1653, ν(C=S) 1228. ^{1}H NMR ($CDCl_3$) δ 8.54 (s, lH, coum C4-*H*), 7.82 (s, lH, coum C5-*H*), 7.77 (dd, lH, *J* = 1.5 Hz, *J* = 9 Hz, coum C7-*H*), 7.31 (d, lH, *J* = 9 Hz, coum C8-*H*), 4.84 (s, 2H, COC*H*,), 3.92, 3.80 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.20-1.99 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 208.1, 202.2, 171.3, 152.4, 138.4, 134.2, 130.1, 124.6, 122.2, 121.0, 53.4, 42.3, 25.0.

14. Yield: 69%. Mp. 207-209°C. Anal. Calcd for $C_{16}H_{16}BrNO_3S_2$: C, 46.38; H, 3.89; N, 3.38. Found: C, 47.06; H, 3.55; N, 3.64%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1740, ν(C=O) 1695, ν(C=S) 1255. ^{1}H NMR ($CDCl_3$) δ 8.42 (s, lH, coum C4-*H*), 7.80 (s, lH, coum C5-*H*), 7.74 (dd, lH, *J* = 1.5 Hz, *J* = 9 Hz, coum C7-*H*), 7.32 (d, lH, *J* = 9 Hz, coum C8-*H*), 4.82 (s, 2H, COC*H*,), 4.03, 3.84 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.22-2.04 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 208.6, 202.2, 171.3, 154.3, 140.1, 135.6, 132.4, 124.6, 123.1, 118.6, 48.1, 43.1, 28.4, 24.0.

15. Yield: 75%. Mp. 201-203°C. Anal. Calcd for $C_{17}H_{18}BrNO_3S_2$: C, 47.67; H, 4.24; N, 3.27. Found: C, 46.27; H, 4.75; N, 3.30%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1737, ν(C=O) 1685, ν(C=S) 1238. ^{1}H NMR ($CDCl_3$) δ 8.52 (s, lH, coum C4-*H*), 7.81 (s, lH, coum C5-*H*), 7.77 (dd, lH, *J* = 1.5 Hz, *J* = 9 Hz, coum C7-*H*), 7.30 (d, lH, *J* = 9 Hz, coum C8-*H*), 4.67 (s, 2H, COC*H*,), 3.68, 3.60 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.10-1.90 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 207.3, 201.5, 169.7, 149.0, 135.5, 132.7, 129.0, 123.1, 121.7, 120.2, 65.5, 49.4, 43.1.

16. Yield: 88%. Mp. 204-206°C. Anal. Calcd for $C_{16}H_{16}BrNO_4S_2$: C, 44.66; H, 3.75; N, 3.25. Found: C, 45.13; H, 3.48; N, 3.51%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1741, ν(C=O) 1689, ν(C=S) 1230. ^{1}H NMR ($CDCl_3$) δ 8.32 (s, lH, coum C4-*H*), 7.75 (s, lH, coum C5-*H*), 7.71 (dd, lH, *J* = 1.5 Hz, *J* = 9 Hz, coum C7-*H*), 7.24 (d, lH, *J* = 9 Hz, coum C8-*H*), 4.71 (s, 2H, COC*H*,), 3.80, 3.68 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.15-1.97 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 207.2, 201.5, 169.6, 149.0, 135.0, 132.1, 129.3, 123.6, 121.0, 120.1, 68.1, 51.3, 43.1.

17. Yield: 61%. Mp. 184-186°C. Anal. Calcd for $C_{16}H_{16}BrNO_3S_3$: C, 43.05; H, 3.61; N, 3.14. Found: C, 43.54; H, 3.58; N, 3.34%. IR (KBr pellet, cm^{-1}) ν(C=O ring) 1737, ν(C=O) 1674, ν(C=S) 1238. ^{1}H NMR ($CDCl_3$) δ 8.40 (s, lH, coum C4-*H*), 7.81 (s, lH, coum C5-*H*), 7.75 (dd, lH, *J* = 1.5 Hz, *J* = 9 Hz, coum C7-*H*), 7.21 (d, lH, *J* = 9 Hz, coum C8-*H*), 4.68 (s, 2H, COC*H*,), 3.77, 3.64 (t, *J* = 7 Hz, 2H each, pyr H2, H5), 2.05-1.87 (m, 4H, pyr H3, H4). ^{13}C NMR ($CDCl_3$) δ 206.4, 200.1, 171.6, 150.2, 137.4, 133.3, 124.8, 122.4, 120.7, 119.7, 49.2, 43.1, 27.1.

4. Antifungal Activity

All the compounds to be tested were dissolved in DMSO at a concentration of 4000 pg/mL and the final concentration was reduced to 200 pg/mL with sterile distilled water. No effect of DMSO (5%) was observed upon growth of dermatophytes. The dermatophyte strains which were grown on slant medium of Sabouraud (Difco) were transferred to 3.5 mL nutrient broth (NB, Diagnostic Pasteur) and incubated for three to five days at 25°C. At the end of the incubation period these strains were transferred into screwcapped bottles containing sterilized beads, and shaken for 4-5 min in a vortex (IKA-VF, Germany). The suspensions of the cultures were adjusted to have an absorbance degree of 0.6 at 450 nm in the spectrophotometer. Eight different dilutions between 25-0.2 μg/mL were prepared in microplates by serial dilutions from top to bottom. Then all the wells except the 12th wells (positive control)

were filled with 10 μL of the standardized strains. These plates were incubated at 25°C for five or six days. The minimum concentration at which no growth was observed was taken as the MIC value. It should be noted, however, that these techniques leave a variable number of broken hyphae, and therefore even an identical optical density of such hyphal suspensions could lead to a considerable variation in the number of viable cells; this would obviously prevent proper standardization of the inoculum.

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